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4373190 02

Patents ADP number (if you know it)

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4. Title of the invention Particulates

5. Name of your agent (if you have one)
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8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request? Yes

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Continuation sheets of this form	0
Description	15
Claim(s)	
Abstract	
Drawing(s)	3

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Priority documents	
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Statement of inventorship and right to grant of a patent (Patents Form 7/77)	
Request for preliminary examination and search (Patents Form 9/77)	
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11. I/We request the grant of a patent on the basis of this application.

Signature(s) Marks & Clerk Date: 12 February 2004

12. Name and daytime telephone number of person to contact in the United Kingdom

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gbp290095

PARTICULATES

The present invention relates to particulates, and in particular to melt extruded multiparticulates which provide controlled release of an active ingredient.

BACKGROUND OF THE INVENTION

Multiparticulates of uniform dimensions with modified drug release properties can readily be manufactured by melt extrusion technology. Melt extrusion is a solvent-free single-step process for manufacturing multiparticulates and is particularly useful for drug release modification. By selection of suitable polymers and additives, melt extrusion technology can be used both to enhance the solubility, and subsequently the bioavailability, of poorly water soluble drugs as well as to retard drug release of moderate to highly water soluble drugs for controlled release products.

The backbone of melt extrusion technology is the application of thermoplastic materials which act as binders for embedded drugs in solution or dispersion form within the matrix. Thermoplastic polymers with low glass transition temperatures (Tg) are preferred for processing by melt extrusion. Lower processing temperatures are also preferred with respect to the stability of heat sensitive drugs and other necessary excipients. Polymer glass transition temperatures can also be further reduced to facilitate processing at lower temperature with optional addition of plasticisers.

Illustratively, WO 9614058 provides a sustained-release pharmaceutical formulation, comprising a melt-extruded blend of a

therapeutically active agent, one or more materials selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, and mixtures thereof; and one or more hydrophobic fusible carriers which provide a further retardant effect and are selected from the group consisting of natural or synthetic waxes, fatty acids, fatty alcohols, and mixtures thereof, the fusible carrier having a melting point from 30 to 200°C. The melt-extruded blend is divided into a unit dose containing an effective amount of said therapeutically active agent to render a desired therapeutic effect and providing a sustained-release of said therapeutically active agent for a time period of from about 8 to about 24 hours.

Furthermore, WO 9614058 describes a method of preparing a sustained-release pharmaceutical extrudate suitable for oral administration. The method comprises:

blending a therapeutically active agent together with (1) a material selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, and mixtures thereof and (2) a fusible carrier selected from the group consisting of natural or synthetic waxes, fatty acids, fatty alcohols, and mixtures thereof; said retardant material having a melting point between 30-200°C and being included in an amount sufficient to further slow the release of the therapeutically active agent,

heating said blend to a temperature sufficient to soften the mixture sufficiently to extrude the same;

extruding said heated mixture as a strand having a diameter of from 0.1 -3 mm;

cooling said strand; and

dividing said strand to form non-spheroidal multi-particulates of said extrudate having a length from 0.1 -5 mm; and

dividing said non-spheroidal multi-particulates into unit doses containing an effective amount of said therapeutically active agent,

said unit dose providing a sustained-release of said therapeutically active agent for a time period of from about 8 to about 24 hours.

In certain preferred embodiments of WO 9614058, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methylmethacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. Thus, in many of the Examples, the hydrophobic material is Eudragit RS PO (poly(ethyl acrylate, methyl methacrylate, trimethylammonium methacrylate chloride), optionally in the presence of Eudragit L100 (poly (methacrylic acid, methyl methacrylate).

Summary of the Invention

According to the present invention, we provide a process for preparing a controlled release pharmaceutical extrudate, wherein the mix for extrusion includes a neutral poly(ethyl acrylate, methyl methacrylate) copolymer.

We also provide controlled release pharmaceutical extrudates containing a neutral poly(ethyl acrylate, methyl methacrylate) copolymer.

Neutral poly(ethyl acrylate, methyl methacrylate) is commercially available in the form of an aqueous dispersion. Two grades, Eudragit NE 30 D and Eudragit NE 40 D, comprise

respectively 30% and 40% of the polymer. These products are used conventionally in the preparation of controlled release coats.

We now find that by utilising such polymers in the preparation of controlled release pharmaceutical extrudates, we obtain melt extruded multiparticulates which exhibit rubber-like characteristics and improve resistance to tamper. Tamper resistance is of especial importance for products containing opioid analgesics or other active ingredients which are subject to abuse.

Rubber-like means compressible without breaking, and preferably resilient.

In one form the multiparticulates may be compressed by hand between two rigid surfaces, e.g. a coin and a table top or between two spoons, without breaking; the multiparticulates may be distorted but do not break or shatter and may, ideally reassume more or less their original shape.

The neutral poly(ethyl acrylate, methyl methacrylate) is suitably employed in an amount of up to 66% in the mix for extrusion, more typically from 20 to 50%, such as 30 to 40% of the extrusion mix.

The neutral poly(ethyl acrylate, methyl methacrylate) can be employed with other ingredients including drug. The reader is referred to WO 9614058, incorporated herein in full by specific reference. The neutral poly(ethyl acrylate, methyl methacrylate) can form all or more preferably part of the hydrophobic material employed in the extrusion method of that patent specification.

In this respect, our preferred compositions include an insoluble ammonium methacrylate polymer. The insoluble ammonium methacrylate polymer is suitably Eudragit RS PO, which is an

ammonio methacrylate. In particular, Eudragit RS PO is a sparingly water permeable thermoplastic polymer which can significantly retard release.

A plasticiser is preferred. The plasticiser is normally chosen from water insoluble solids such as cetyl alcohol, stearyl alcohol and cetostearyl alcohol; water soluble solids such as sorbitol and sucrose and high molecular weight polyethylene glycol, water insoluble liquids such as dibutyl sebacate and tributyl citrate and water soluble liquids such as triethyl citrate, propylene glycol and low molecular weight polyethylene glycol. Stearyl alcohol is a preferred plasticiser. Another preferred plasticiser is a high molecular weight polyethylene glycol such as PEG 6000.

A lubricant is preferred. The lubricant is normally a solid, and is suitably chosen from stearic acid, glyceryl behenate, magnesium stearate, calcium stearate, talc and silicone dioxide (fused silica). The presence of lubricant in the melt extrusion formulation improves blending, kneading conveying and reduces cohesion and adhesion forces. Smooth extrusion at low to moderate temperatures improves batch to batch reproducibility and reduces the strain on both the product and equipment. Stearic acid, possibly in the form of a salt, is a preferred lubricant. Another preferred lubricant is glyceryl behenate.

A drug is usually present in the multiparticulates. The reader is referred to WO 9614058 for examples. Oxycodone is a typical drug for use in the products and processes of this invention.

Suitable percentage amounts for the preferred ingredients are given in the following table, based on the total weight of the specified ingredients:

	typical range	preferred range
water-insoluble neutral poly(ethyl acrylate, methyl methacrylate)	5 to 66	20 to 50
drug	0* to 50	5 to 40
water-insoluble ammonium methacrylate polymer	0 to 85	35 to 75
plasticiser	0 to 30	3 to 25
lubricant	0 to 25	2 to 25

* the amount of drug can be 0% in placebo formulations.

Other additives may also be employed to produce multiparticulates within a set of predetermined specifications. Bulking agents for example lactose, microcrystalline cellulose and calcium phosphate, are widely used pharmaceutical excipients and can be used in the present invention to modify the release rates and/or total release. Other release modifying agents may also be considered to modulate the release rate and/or enhance total release.

The multiparticulates are preferably produced by a process comprising the following steps:

(a) granulation, generally wet granulation

(b) extrusion of the granulate

(c) drying, preferably by means of a fluidised bed drier

(d) optionally milling the dried particles

(e) melt extrusion of the product from step (c) or (d)

The granulation step may be carried out using conventional procedures for example using a high shear mixer such as a Gral. The dry ingredients are added first, these are mixed by operation of the

mixer and then the dispersion of polymer is added by spraying or dropwise, and mixing continued.

The granulate is then extruded, for example, using an Alexanderwerk extruder. The extrudate is then dried using preferably a fluidised bed dryer. The extrudate may be produced directly of a suitable size for fluidised bed drying using a suitable extruder such as the aforementioned Alexanderwerk where the small blade breaks up the pellets, or may be broken down to a suitable size.

The dried material will typically contain less than 5% $^{w}/_{w}$ water e.g. 2-3% $^{w}/_{w}$, or even trace amounts.

The melt extrusion process may be carried out in a manner similar to that described in WO 9614058.

For the present invention, we prefer to employ a twin screw extruder. Essentially, the blend as a powder or granules is fed by a feeder into the first segment of the barrel at relatively low temperature (10-20°C) to ensure a constant flow of material to the high temperature barrels. The feeder provides a uniform current of the blend to the extruder. Consistency is desirable as irregular and variable feeding rates can produce multiparticulates with various physical properties, such as density and porosity.

The preferred twin extruder is designed with twin screws, preferably counter-rotating screws, for the task of conveying, blending, compressing, heating and plastifying the blend. The screws which perform a significant part of this melt extrusion process are built of different smaller elements. Mixing and kneading time can be significantly altered by changing the type, length and configuration of the screws elements. Short residence times and moderate to low

shear forces contribute to safe processing and stable product even with heat sensitive drugs.

Screw rotating speeds may play a part in the quality of the multiparticulates produced. High rotation speeds without appropriate compensation of the feed rate may produce high porosity multiparticulates with a variable drug release rate. On the other hand slow screw rotation would induce unnecessary long residence times. A vacuum connected to the extruder barrel is desirable to remove trapped air within the plastified material and thus produce dense non-porous multiparticulates.

The extrusion head is typically designed to produce multiple strands of fixed diameter, for example 1.0 mm. The number, shape and diameter of the orifices can be changed to suit a predetermined specification.

In addition to the screw speed, the other main influential parameters are the screw torque, individual barrel temperature, and extrusion head pressure and temperature.

In accordance with one cutting procedure of this invention, the extruded strands are carried away from the die-head on a conveyer. The strand diameter is affected by the die-head orifice diameter, the screws speed, barrel temperature and conveying speed. Conveying is appropriate to carry the extruded strand to a laser gauge or other measuring device. During this conveying process the strands cool down gradually, but essentially remain flexible. Flexible strands retain integrity on the laser gauging device, between the pelletiser feed nip rolls and during entry to the pelletiser. Rapidly cooled strands, depending on the formulation, may lose their integrity and shatter during passage through the nip rolls and pelletiser into uneven-shaped and irregular-sized multiparticulates.

A laser gauge may be used to provide a continuous measurement of strand diameter. Parameters which affect the strand diameter include starting material feed rate, screw speed, conveyer belt speed and nip rolls speed.

The measured strands are fed into the pelletiser by nip rollers. The pelletiser cuts the fed strands, for instance using a rotary knife cutter, to a pre-determined length, for example 1.0 mm. The feeding rate of the strands and the pelletiser cutter speed determine the length of the multiparticulates.

Overall, the co-ordination/interaction between the feeder, extruder, conveyor, laser gauge and pelletiser is an important parameter affecting the quantity, quality and reproducibility of the final multiparticulate products.

Multiparticulates produced by this cutting procedure where the extruded strands are carried away from the die-head typically take the form of cylinders.

In another preferred cutting procedure, a cutter cuts the extruded mix as it emerges under pressure and still molten from the orifices of the die plate. The cutter is suitably a rotary cutter with one or more blades which sweep over the surface of the die head to pass the orifices. Two diametrically opposed blades are preferred. Ideally, the outer surface of the die-head is coated with a non-stick materisl, e.g. polytetrafuoroethylene (PTFE). As the cut extrudate particles expands and cool, they tend to form rounded surfaces. By appropriate adjustment of the rate of extrusion and the speed of the cutter blade, it is possible to arrange for spherical or substantially spherical multiparticulates to be obtained. In one embodiment a stream of air is direwcted at the surface of the die-head, the air being

directed at a reduced temperature to cool the extrudate and to speed solidification.

Spherical multiparticulates produced by this method offer a number of advantages:

Better batch to batch reproducibility.

Easier coating and lower coating weight required.

Better capsule filling and higher yield.

More stable at elevated temperature.

More tamper resistant.

Reduce or eliminate some problems that arise during conveying and pelletising the strands such as strands shattering to different length pellets and static charge.

The multiparticulates may be divided into unit doses such that each individual unit dose includes a dose of drug for adminstration to a mammal, preferably a human patient. For the preferred drug, oxycodone, a suitable dose of oxycodone is 5 to 400 mg, especially 5 mg, 10 mg, 20 mg, 40 mg, 80 mg or 160 mg unit dosages. In this respect, a unit dose contains an effective amount of the therapeutically active agent to produce pain relief and/or analgesia to the patient. The dose of oxycodone administered to a patient will vary due to numerous factors, including the weight of the patient, the severity of the pain, the metabolic status and the nature of any other therapeutic agents being administered

The resultant multiparticulates can be employed as a fill in a capsule. Thus, the present invention provides a capsule suited for once or twice a day dosing. Other dosage forms of the controlled release formulation can be provided.

In one preferred embodiment, the multiparticulates are filled into gelatin capsules each containing a unit dose. The fill weight in

the capsule is preferably in the range 80 to 500 mg, more preferably 120 to 500 mg. In a variation of this invention, the unit doses of multiparticulates may be incorporated into other solid pharmaceutical dosage formulations, for example using compression or shaping into tablets, or by forming the extruded product into the form of a suppository.

The preferred capsules or other unit dose forms of this invention preferably are designed for administration at intervals of about 12 hours.

The preferred drug for inclusion in the multiparticualtes is oxycodone. The unit dose form then suitably has an oxycodone dissolution rate *in vitro*, when measured by the USP Paddle Method (see the U.S. Pharmacopoeia XXII 1990) at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C of between 12.5 and 42.5% (by wt) oxycodone released after 1 hour, between 25 and 56% (by wt) oxycodone released after 2 hours, between 45 and 75% (by wt) oxycodone released after 4 hours and between 55 and 85% (by wt) oxycodone released after 6 hours. Furthermore, we prefer that the peak plasma level of oxycodone obtained *in vivo* occurs between 2 and 4.5 hours after administration of the dosage form.

More information on desirable characteristics for such oxycodone formulations is given in WO 9310765 which is incorporated herein in full by specific reference.

As an alternative, the oxyocodone capsules or other unit dose forms of this invention are designed for administration at intervals of about 24 hours. To this end, the unit dose form suitably has an oxycodone dissolution rate *in vitro*, when measured by the USP Basket Method at 100 rpm in 900 ml aqueous buffer at a pH between 1.6 and 7.2 at 37°C of from 0% to about 40% at 1 hour, from about 8% to

about 70% at 4 hours, from about 20% to about 80% at 8 hours, from about 30% to about 95% at 12 hours, from about 35% to about 95% at 18 hours, and greater than about 50% at 24 hours. Furthermore, we prefer that the peak plasma level of oxycodone obtained *in vivo* is reached at about 2 hours to about 17 hours after administration at steady state of the dosage form.

More information on desirable characteristics for such oxycodone formulations is given in WO 02087512 which is incorporated herein in full by specific reference.

In a variation, the present invention provides unit doses which contain oxycodone and an oxycodone antagonist effective to prevent tampering. In this respect, reference is made to WO 0313433 which is incorporated herein in full by specific reference. In particular, the unit dose can contain oxycodone and naltrexone.

To this end, the present invention provides melt extruded multiparticulates of oxycodone, and melt extruded multiparticulates of oxycodone antagonist such as naltrexone. The naltrexone multiparticulates do not release naltrexone on conventional administration, and for example have a non-release coating. Both populations are preferably visually and physically identical.

An important aspect of this invention is a capsule with a unit dose fill of less than 500 mg, comprising up to about 350 mg of oxycodone multiparticulates, and up to about 200 mg of tamper-proof oxycodone antagonist. For example, there can be 120 to 300 mg of oxycodone multiparticulates, and 125 to 175 mg of tamper-proof oxycodone antagonist multiparticulates.

SUMMARY OF THE DRAWINGS

Reference is made in the following experimental section to the accompanying drawings, in which:

Figure 1 shows the die-head of a melt extruder.

Figure 2 shows a rotary cutter for use with the die-head of Figure 1.

Figure 3 shows the product of batch F721/74.

EXAMPLE OF THE INVENTION

Example 1

Three batches F743/84, F743/88 and F746/76 were manufactured following a similar procedure:

Step 1. Initially, the following items were placed into a Gral 10 high shear mixer, pre-heated to 40°C, and dry blended at high speed for 2 minutes:

Oxycodone Hydrochloride
Eudragit RSPO
Stearyl Alcohol
Stearic Acid

Step 2. The Eudragit NE40D dispersion was screened through a 350 micron mesh to eliminate aggregates and transferred into a suitably sized container.

Step 3. The screened Eudragit NE40 dispersion was sprayed at low atomising pressure onto the dry blended materials from step 1 in the mixing bowl, whilst maintaining mixing / chopping.

Step 4. The application of Eudragit NE40D was continued until granule formation occurred.

Step 5. The application of Eudragit NE40D was periodically halted to scrape the sides of the mixing bowl.

Step 6. After all the Eudragit NE40D had been applied, the granules were dried under the same temperature conditions and at reduced mixing / chopping speeds.

Step 7. The dried granules were cooled to room temperature and collected.

Step 8. The granule were then fed at a controlled rate to a Leistritz 18 extruder equipped with a conveyor and pelletiser. The extruder had a 1.5 mm die plate, and heated Stations as follows, Stations 3 to 8 90°C to 100°C, Stations 9 and 10 100°C. The feed rate was 2.0 to 2.6 kg/hr and the screw speed 100 to 141 rpm, with a torque/melt pressure of 50-60% / 40-50 bar.

The extruded strands are carried away from the die-head on a conveyer and cut into cylindrical multiparticulates.

Material	Batch No./% w/w		
	F743/84	F743/88	F746/76
Lactose anhydrous	10.0	10.0	
Oxycodone hydrochloride			10.0
Eudragit RS PO	40.0	32.0	32.0
Stearyl alcohol	10	10.0	10.0
Stearic Acid	6.0	6.0	6.0
Eudragit NE*	34.0	42.0	42.0
Total	100	100	

*As Eudragit NE 40D (water removed by drying)

Example 2

For this example, the alternate cutting procedure was employed. Extrudate emerges from the twelve orifices of the die head shown in Figure 1 of a Leistritz 18 extruder. A rotary cutter with two blades, as shown in Figure 2, is used to cut the extruded mix as it emerges under pressure and still molten from the orifices of the die plate. The blades sweep over the surface of the die-head to pass the orifices. As they expand and cool, the cut extrudate particles tend to form rounded surfaces

The following formulation was employed to produce placebo product containing lactose as a pharmaceutical non-active ingredient.

Material	Batch No./% w/w
	F721/74
Lactose anhydrous	10.0
Eudragit RS PO	37.0
Stearyl alcohol	10.0
Stearic Acid	6.0
Eudragit NE 40D	37.0
Total	120.0

By appropriate adjustment of the extrusion parameters including temperature and rates of extrusion, spherical or substantially spherical multiparticulates may be obtained (see Figure 3).

Figure 1

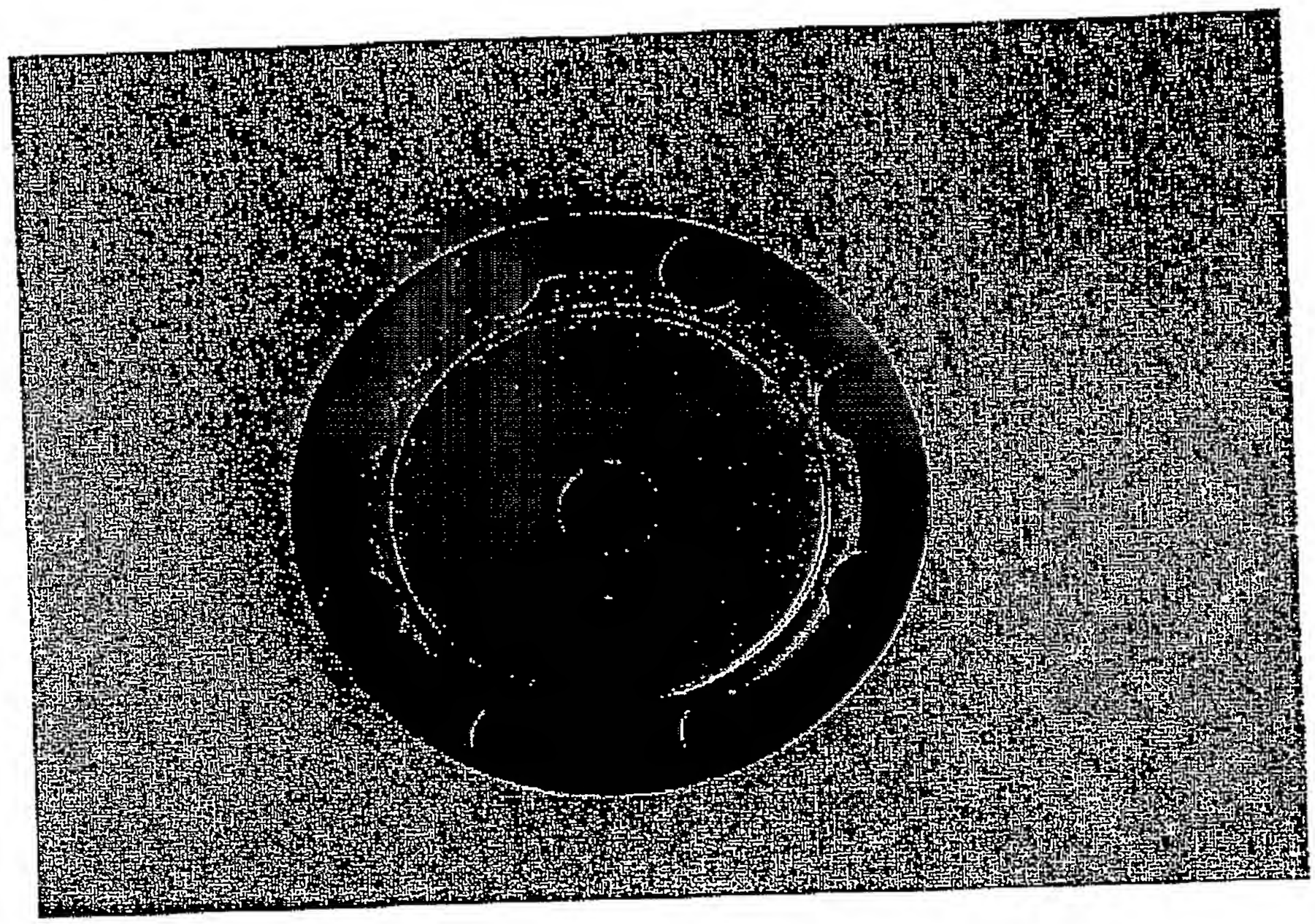

Figure 2

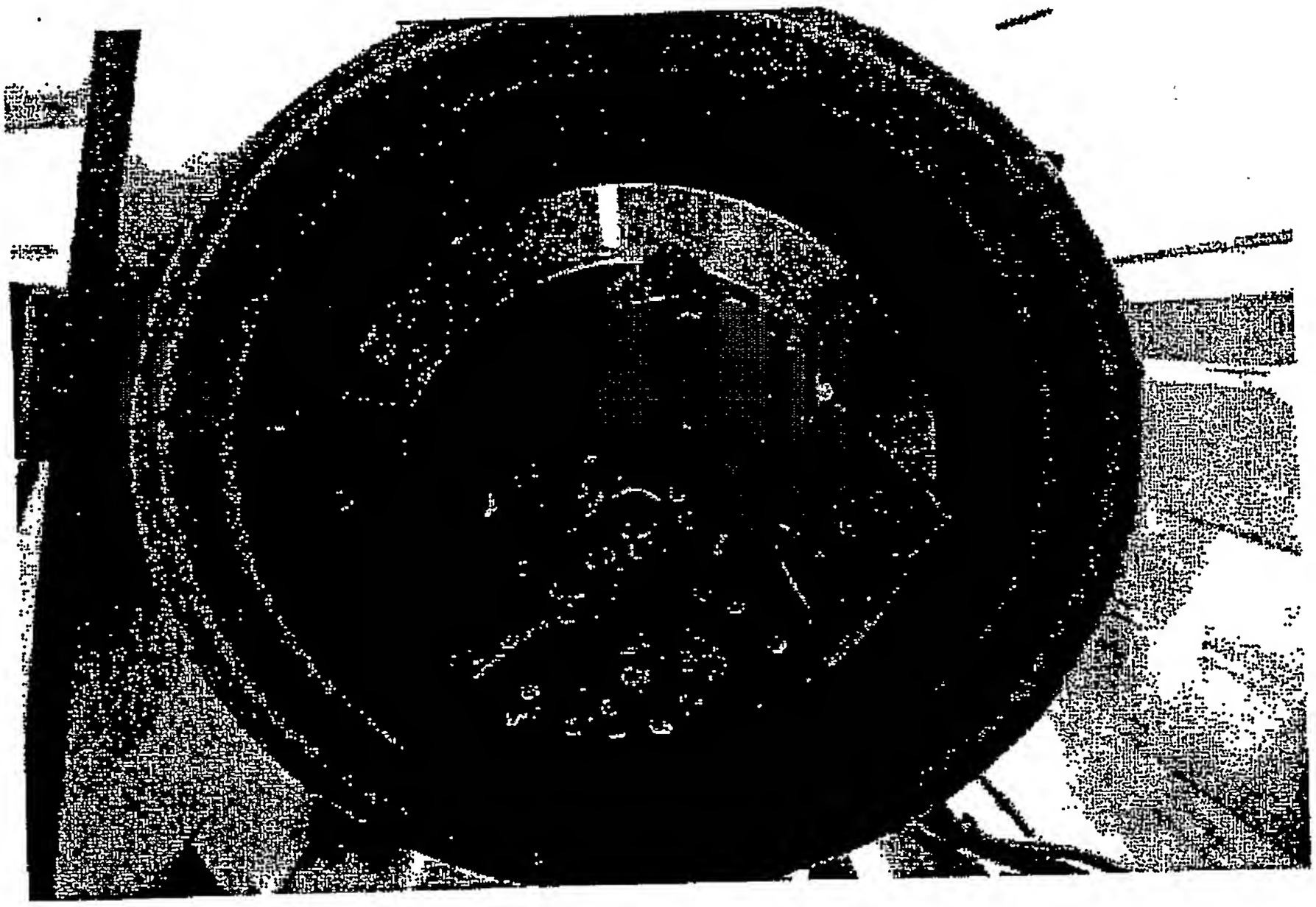

Figure 3